

Clinical Development

CAIN457/Secukinumab/Cosentyx[®]

Clinical Trial Protocol CAIN457F2304 / NCT03031782

A three-part randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of secukinumab treatment in Juvenile Idiopathic arthritis subtypes of psoriatic and enthesitis-related arthritis

Statistical Analysis Plan (SAP) Amendment 4

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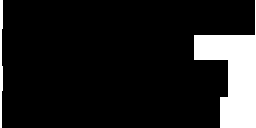











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Document History – Changes compared to previous final version of SAP

Date	Reason for update	Outcome for update	Section and title impacted (Current)
12-Mar-2020			
	Protocol deviation period can't be derived, since the date was not collected.	Protocol deviation summary is overall (not by treatment period).	2.3.1 Patient disposition
	Novartis request to remove prohibited medication summary, since the analysis is not required.	Removed summary of prohibited medication. Also, updated medications are coded according to the Novartis Drug and Therapy Dictionary (NovDTD) and non-drug therapies are by MedDRA.	2.4.2 Prior and concomitant medications/therapies
	Corrected typo.	Corrected ACZ to AIN457. Updated plot from 'cumulative probability to stay flare free' to 'cumulative probability to flare'.	2.5.2 Statistical hypothesis, model, and method of analysis
	Request from clinical team.	JIA ACR response plots added for TP1 and TP2. Also, mean percent improvement from baseline to Week 12 plot for JIA ACR core components other than CRP added. For CRP, use median percent change. Also, added JADAS-27 and JADAS-71 change from baseline plots for TP1.	2.6 Analysis of secondary objectives
			
	Novartis programmer/statistician request to remove, since the listing is not required.	Removed sentence "For those subjects who received not the treatment randomized, i.e. who received erroneously the wrong	2.8 Safety analyses

Date	Reason for update	Outcome for update	Section and title impacted (Current)
		treatment at least once, an additional adverse event (AE) listing will be prepared displaying which events occurred after the treatment errors.”	
	Updated per data collected.	The ratio “apolipoprotein B / apolipoprotein A1” can’t be derived since the components weren’t collected.	2.8.2 Laboratory data
	AIN457 program level update, based on previous DMC feedback.	Vital signs notable criteria updated.	2.8.3 Vital signs
	 JADAS – corrected per reference papers.	 Derivation of JADAS updated per reference papers.	
			
22-Jun-2020	Added clarification	Added clarification of when TP2 will be considered complete.	1.1 Study design
	Additional important stratification factor identified.	Primary  updated to include MTX use at baseline as a stratification factor.	2.5.2 Statistical hypothesis, model, and method of analysis  4 Change to protocol specified analyses 5.2.1 Analysis of continuous data 
			

Date	Reason for update	Outcome for update	Section and title impacted (Current)
	Required analysis updated.	<p>Added percent change from baseline for JIA ACR core components.</p> <p>Dropped all "Overall" tables for JIA ACR 30/50/70/90/100 and inactive disease status.</p> <p>JIA ACR 30/50/70/90/100 line graph only for TP1 and not TP2 or overall.</p> <p>Added bar chart of JIA ACR 30/50/70/90/100 response at the end of Treatment period 2 and corresponding table.</p> <p>Removed descriptive statistics for each JIA ACR core component without LOCF.</p>	2.6 Analysis of secondary objectives
	Additional analysis required. Required analysis updated.	<p>Added analysis for Clinicaltrials.gov and EudraCT.</p> <p>Cumulative events rate was replaced by flare-free rate.</p> <p>Options 'reduceout' and 'timelist' added to the proc lifetest.</p>	2.8.1 Adverse events (AEs) 5.2.1.2 Kaplan-Meier analysis
13-Oct-2020			

Date	Reason for update	Outcome for update	Section and title impacted (Current)
	Consistent with SCS.	'Entire study' updated to 'Entire treatment period' throughout.	2.2 Analysis sets and treatment groups 2.8 Safety analysis 2.13 Summary of statistical analysis
	Entire treatment period analysis added.	Added entire treatment period in the treatment groups description.	2.2.1 Treatment groups
	Remove wording about Rescue medication analysis, since not required. Added disposition for follow-up.	Remove wording about Rescue penalty medication analysis. Also, added disposition table for the follow-up period.	2.3.1 Patient disposition
	Consistent with SCS.	Added duration of exposure (days) table for the entire treatment period.	2.4.1 Study treatment / compliance
	Correct that MTX is not a stratification variable, but only another factor in the model.	MTX is not a stratification factor in the study, therefore, correct the description about MTX by removing it as a "stratification factor".	2.5.2 Statistical hypothesis, model, and method of analysis 2.6.4 Analysis of secondary objectives 5.2.1 Analysis of continuous data
	Consistent with SCS.	Added Treatment Period 3 in safety analysis. Also, replaced tables of exposure adjusted incidence of AEs during Treatment period 2 with tables for the entire treatment period.	2.8.1 Adverse events (AEs) 2.8.2 Laboratory Table 1-9 Summary of Safety analysis by treatment period and statistical method
	Since, Cosentyx has been marketed the SPP is replaced by RMP.	In Clinicaltrials.gov and EudraCT section Removed text about dry run and clarified 0-5%. Safety Profiling Plan (SPP) replaced by Risk Management plan (RMP). Location of Program Case Retrieval Sheet updated and note about primary and secondary system organ classes updated.	2.8.5 Compound specific safety evaluation
	In the CRF, if the patient has early discontinuation, it will state either "week 12"	The early discontinuation week will be re-mapped to the next visit of last scheduled visit based on the assessments.	5.1 Visit Windows

Date	Reason for update	Outcome for update	Section and title impacted (Current)
	or “week 104” instead of the actual early discontinuation week.		
3-Dec-2020			
	Criteria not required in protocol or standard.	Removed criteria ‘ALT or AST >8xULN & TBL >2xULN’.	2.8.2 Laboratory data
	Overview of subjects with anti-drug antibodies table can be derived programmatically and reviewed by the medical writer.	For overview of subjects with anti-drug antibodies summary replaced text ‘will be provided as an in-text table by the medical writer’ with ‘ will be summarized’.	2.8.4 Immunogenicity
	Clarification.	Minor update to SAS code to clarify timelist will also be produced at days 28, 56, 84, etc.	5.2.1.2 Kaplan-Meier analysis

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List of abbreviations

ACR	American College of Rheumatology
AE	Adverse Event
AJC	Active joints count
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BP	Blood pressure
████	████████████████████
CHAQ	Childhood Health Assessment Questionnaire
CMH	Cochran-Mantel-Haenszel
CRF	Case Report/Record Form (paper or electronic)
CRP	C-reactive Protein
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DBL	Database lock
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report/Record Form
ERA	Enthesitis-Related Arthritis
ESR	Erythrocyte sedimentation rate
████	██
FAS	Full analysis set
GGT	Gamma-glutamyl transferase
GPS	Global Programming and Statistics Environment
HDL	High-density lipoprotein
HGB	Hemoglobin
IGA	Investigators Global Assessment
IVR	Interactive Voice Response
JADAS	Juvenile Arthritis Disease Activity Score
JIA	Juvenile Idiopathic Arthritis
JPsa	Juvenile Psoriatic Arthritis
████	██
KM	Kaplan-Meier
LDL	Low-density lipoprotein
LFT	Liver function test
LLN	Lower Limit of Normal
LLQ	Lower level of quantification
LOCf	Last Observation Carried Forward
LPLV	Last Patient Last Visit
MCP	Metacarpophalangeal

MedDRA	Medical dictionary for regulatory activities
MTX	Methotrexate
NovDTD	Novartis Drug and Therapy Dictionary
OMU	Original measurement unit
PD	Protocol deviation
PDS	Programming Dataset Specification
PGA	Physician global assessment
PIP	Proximal interphalangeal
PK	Pharmacokinetics
PsA	Psoriatic Arthritis
PRO	Patient Reported Outcome
PT	Preferred Term
RMP	Risk Management Plan
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
s.c.	Subcutaneous
SCS	Summary of clinical safety
SD	Standard deviation
SI	International standard
SJC	Swollen Joint Count
SMQ	Standardized MedDRA Query
SOC	System organ class
SPP	Safety Profiling Plan
TBL	Serum total bilirubin
TEAE	Treatment emergent adverse event
TFL	Tables, Figures and Listings
TG	Triglycerides
TJC	Tender Joint Count
TPx	Treatment Period x
ULN	Upper limit of normal
ULQ	Upper Level of Quantification
VAS	Visual Analogue Score

1 Introduction

Data will be analyzed by [REDACTED] according to this SAP and the data analysis section 9 of the amended clinical study protocol V02. The statistical methodology is described below and any deviations from the protocol are documented. Additional detailed information regarding the analysis methodology is contained in the Appendix section. The analysis plan for DMC will be prepared separately.

1.1 Study design

This is a double-blind, placebo-controlled, event-driven randomized withdrawal study to investigate the efficacy and safety of secukinumab treatment in the JIA categories of JPsA and ERA. The study is divided into 3 parts (plus a post-treatment follow-up period) consisting of open-label, single-arm active treatment in Treatment Periods 1 and 3 and a randomized, double-blind, placebo controlled, event-driven withdrawal design in Treatment Period 2, as described below:

Treatment Period 1 (TP1): A maximum 8-week screening period is used to assess patient eligibility. All eligible patients will enter Treatment Period 1 to receive 12-weeks of open-label secukinumab at a dose predicted to achieve secukinumab serum levels equivalent to adults administered a 150 mg dose regimen. Secukinumab will be administered subcutaneously (s.c.) weekly for the first 4 weeks (Baseline, Weeks 1, 2, 3, 4) and then every 4 weeks thereafter. Clinical response (JIA ACR 30) will be assessed at Week 12. Responders will advance to Treatment Period 2 and non-responders must exit the trial (early termination visit and enter into the Post-treatment follow-up period).

Treatment Period 2 (TP2): Patients with a clinical response (JIA ACR30) at Week 12 will enter double-blind withdrawal Treatment Period 2 to be randomized 1:1 to either secukinumab or placebo on that visit. Treatment Period 2 is event driven and will close when 33 patients experience a disease flare as per JIA definition. If Treatment Period 2 is closed when a patient becomes eligible to enter Treatment Period 2, the patient will skip Treatment Period 2 and advance directly to Treatment Period 3. When the 33rd flare is observed, all investigators will be informed that Treatment Period 2 is closed and all remaining patients will enter Treatment Period 3 at their next scheduled visit. Because Treatment Period 2 is event driven, it is possible that a patient remains in Treatment Period 2 for the duration of the study (Week 104) before 33 disease flares are observed. Such patients will complete the study without having entered Treatment Period 3.

Treatment Period 3 (TP3): Patients experiencing a disease flare in Treatment Period 2 will immediately enter Treatment Period 3 to receive open label secukinumab every 4 weeks until total study duration of 104 weeks for that patient is achieved. Additionally, when Treatment Period 2 closes, all remaining patients in Treatment Period 2 will enter Treatment Period 3 at their next scheduled visit and all remaining Treatment Period 1 patients who become eligible to enter Treatment Period 2 will skip Treatment Period 2 and enter Treatment Period 3 directly. Consequently, the starting time point of Treatment Period 3 for each patient may be different.

Post-treatment follow-up: All patients completing the study (Week 104) or who discontinue early will enter the Post-treatment follow-up period lasting 12 weeks from the last study drug

dose administration. Only patients who qualify and enter the secukinumab extension trial without interruption of treatment will not require this Post-treatment follow-up visit.

[REDACTED]

The primary endpoint analysis will be performed as part of the final analysis when all patients have completed Week 112 Visit in the post-treatment follow-up period, or entered into extension study after Week 104 Visit, or prematurely discontinued the study, whichever is later.

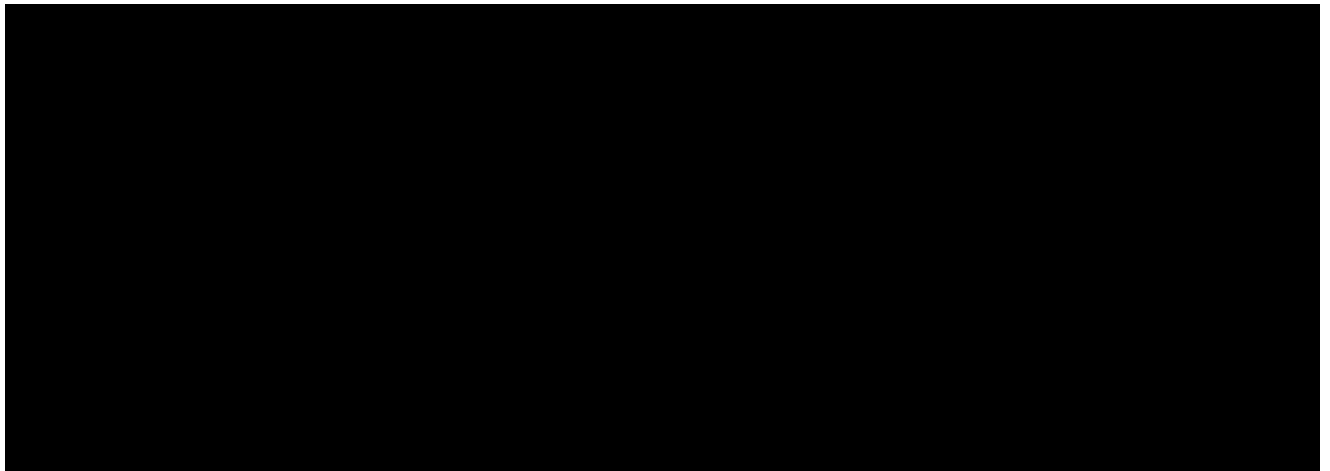
1.2 Study objectives and endpoints

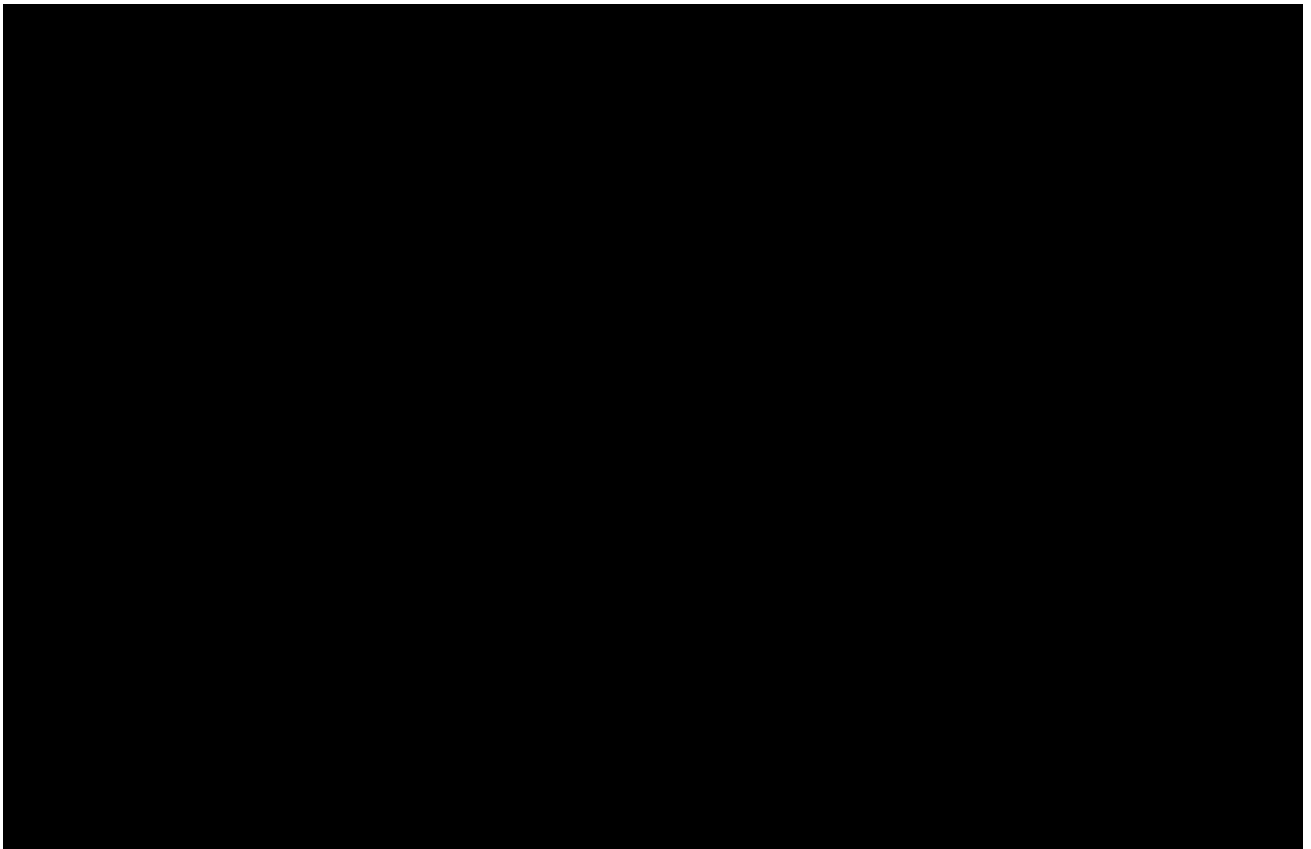
1.2.1 Primary objective

To demonstrate that the time to flare in Treatment Period 2 is longer with secukinumab for combined ERA and JPsA groups than with placebo.

1.2.2 Secondary objectives

1. To evaluate effect of secukinumab treatment for all patients and each JIA category in Treatment Period 1 up to Week 12 (end of Treatment period 1) with respect to:
 - JIA ACR 30/50/70/90/100 and inactive disease status
 - Each JIA ACR core component
 - Change from baseline Juvenile Arthritis Disease Activity Score (JADAS) score
 - Total enthesitis count
 - Total dactylitis count
2. To evaluate withdrawal effect of secukinumab treatment for all patients and each JIA category during and at the end of Treatment Period 2 with respect to:
 - JIA ACR 30/50/70/90/100 and inactive disease status
3. To evaluate Pharmacokinetics (PK) of secukinumab and confirm the predicted dose in Treatment Period 1
4. To evaluate the safety/tolerability and immunogenicity of Secukinumab





2 Statistical methods

2.1 Data analysis general information

Summary statistics for continuous variables include N, mean, standard deviation, minimum, lower quartile, median, upper quartile, and maximum. For binary or discrete variables, the absolute number of subjects in each category and relative frequencies will be provided.

Unless otherwise specified, p-values will be presented as 2-sided p-values and the type I error rate (alpha) will be 5%.

Efficacy and safety data will be presented by treatment period and treatment groups.

2.2 Analysis sets and treatment groups

The following analysis sets will be used for the data analysis.

Randomized set: The randomized set will be defined as all subjects who were randomized at the beginning of TP2. The subjects who participated in TP1 only or TP1 and TP3 only will not be included in the Randomized set. Unless otherwise specified, mis-randomized subjects (mis-randomized in Interactive Voice Response (IVR)) will be excluded from the randomized set.

Mis-randomized subjects are defined as those subjects who were mistakenly randomized into the IVR for TP2 and to whom no randomized study medication was given. Mis-randomized patients will be considered as prematurely discontinued and completed treatment period 1.

The Full Analysis Set (FAS) for Treatment Period 1 (Full Analysis Set 1) will consist of all patients who received at least one dose of study drug in Treatment Period 1.

The FAS for Treatment Period 2 (Full Analysis Set 2) will consist of all randomized patients who received at least one dose of study drug in Treatment Period 2. Following the intent-to-treat principle, patients will be analyzed according to the treatment they were assigned to at randomization in Treatment Period 2.

The FAS for Treatment Period 3 (Full Analysis Set 3) will consist of all patients who received at least one dose of study drug in Treatment Period 3.

The entire treatment period (overall) FAS consists of all subjects who received at least one dose of study drug in the study, this is equivalent to Full Analysis Set 1.

The Safety Set for Treatment Period 1 (Safety Set 1) will consist of all patients who received at least one dose of study drug in Treatment Period 1.

The Safety Set for Treatment Period 2 (Safety Set 2) will consist of all patients who received at least one dose of study drug in Treatment Period 2.

The Safety Set for Treatment Period 3 (Safety Set 3) will consist of all patients who received at least one dose of study drug in Treatment Period 3.

Patients in Safety Set 1, 2 and 3 are analyzed according to treatment received.

The entire treatment period (overall) Safety Set consists of all subjects who received at least one dose of study drug in the study, this is equivalent to Safety Set 1.

There is no Per-Protocol Analysis Set.

2.2.1 Treatment groups

The treatment groups in each treatment period are as follows:

- TP1 - AIN457
- TP2 - AIN457, Placebo in TP2, total
- TP3 - AIN457 (include those not randomized), Placebo in TP2, total
- Entire treatment period (Overall) for efficacy data includes Treatment Period 1, 2 and 3. Entire treatment period will use the same treatment groups as TP3.
- Entire treatment period (Overall) for safety data includes Treatment Period 1, 2 and 3 and Follow-up Period. Entire treatment period will use the same treatment groups as TP3.

AIN457 for entire treatment period refers to all subjects without taking any placebo (including subjects who did not enter Treatment Period 2 (TP2)) and Placebo refers to all subjects taking placebo in TP2. For entire treatment period (overall) and for Treatment Period 3 analysis; subjects with placebo in TP2 and AIN457 in TP3 will be included in the 'Placebo in TP2' and in the 'Total' columns and will not be included in the 'AIN457' column.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

Patient disposition will be presented by Treatment Period and treatment group, also the follow-up disposition will be presented. The number of subjects screened will be presented. In addition, the reasons for screen failures will be provided. The number and percentage of subjects in the Safety Set who completed the study periods and who discontinued the study prematurely (including the reason for discontinuation) during or at end of each Treatment Period will be presented for each treatment period, each treatment group and all subjects.

For each protocol deviation (PD), the number and percentage of subjects for whom the PD applies will be tabulated by treatment group.

The number and percentage of patients in each analysis set will also be tabulated by treatment period and treatment group.

2.3.2 Background and demographic characteristics

Background and disease characteristics at baseline will be summarized descriptively for the Safety Set 1 by the starting treatment (AIN457), and for the Safety Set 2 by the treatment according to randomization in TP2 and by JIA category (ERA and JPsA).

Continuous variables will be summarized by mean, standard deviation, median, minimum, maximum, 25% and 75% quantiles, and number of patients with non-missing data. Categorical variables will be summarized by absolute frequencies and percentages.

Relevant medical history/current medical conditions will be listed and summarized by primary system organ class (SOC) and preferred term of the MedDRA dictionary for the safety set in Treatment Period 1 and according to randomization in Treatment Period 2.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

The exposure to study drug (number of injections) will be summarized by treatment group for the entire treatment period and duration of exposure (days) will be summarized by treatment group and treatment period, and by treatment group for the entire treatment period, both for the Safety Set.

Duration of exposure for the entire treatment period will be defined as the time from first dose of study medication to the last dose plus 84 days or last visit (including follow-up visits) whichever occurs earlier.

2.4.2 Prior and concomitant medications/therapies

The number and percentage of patients taking concomitant medication will be summarized by Anatomical Therapeutic Chemical (ATC) class and preferred term according to the Novartis Drug and Therapy Dictionary (NovDTD). Separate summaries will be provided for therapies that ended prior to Treatment Period 1 (prior therapies) and that were active during Treatment Periods 1, 2 and 3 (concomitant therapies).

The Safety Set corresponding to the study Treatment Period summarized will be used.

Prior medications will be summarized in separate tables by one treatment group for TP1. Concomitant medications will be summarized by treatment groups for TP1, 2 and 3 separately and for all periods together.

Prior medications are defined as treatments taken and stopped prior to first dose of study treatment. Any medication given at least once between the day of first dose of study treatment and the date of within 84 days after last dose will be a concomitant medication, including those which were started pre-baseline and continued into the period where study treatment is administered.

Medications will be presented in alphabetical order, by Anatomical Therapeutic Classification (ATC) codes and grouped by anatomical main group. Tables will show the overall number and percentage of subjects receiving at least one treatment of a particular ATC code and at least one treatment in a particular anatomical main group.

Significant prior and concomitant non-drug therapies and procedures will be summarized by primary system organ class and MedDRA preferred term.

2.5 Analysis of the primary objective

2.5.1 Primary endpoint

The primary efficacy endpoint will be time to disease flare event in Treatment Period 2, which is defined as the interval between the date of randomization to the date of first occurrence of disease flare event. The analysis of the primary efficacy endpoint will be based on the FAS Treatment Period 2.

All subjects who enter Treatment Period 2 will be followed until the sooner of either experiencing a disease flare or the end of Treatment Period 2 when at least 33 flare events are observed and treatment period 2 is completed. Subjects who have not experienced flare event at the end of Treatment Period 2 (as defined in Section 3.1 of the protocol) or discontinue prematurely from Treatment Period 2 before it closes for reasons other than experiencing a disease flare will be censored at the date of the last non-missing flare evaluation (i.e. flare=no evaluation) in Treatment Period 2.

For patients with disease flare, the time to event is computed as follows:

(date of disease flare – date of randomization + 1)

For patients with no disease flare or discontinued, the time to event is computed as follows:

(date of last non-missing flare evaluation (i.e. flare=no) in Treatment Period 2 – date of randomization + 1)

and is considered as censored.

2.5.2 Statistical hypothesis, model, and method of analysis

The primary objective for Treatment Period 2 of the study is to show superiority of secukinumab over placebo regarding the primary variable in Treatment Period 2.

The following statistical hypothesis will be tested once the required number of flares has been observed and when the study has been stopped:

$$H_0: 1 - S_{AIN457}(t) \geq 1 - S_{Pla}(t)$$

$$H_A: 1 - S_{AIN457}(t) < 1 - S_{Pla}(t)$$

at each time point t , with $S_{AIN457}(t)$ and $S_{Pla}(t)$ being the survivor functions in the secukinumab and placebo treatment group at time t .

The two treatment groups will be compared using a one-sided stratified Log-rank test with the stratification factor of JIA category (ERA or JPsA) and another factor MTX use at baseline (yes or no) at the 2.5% level of significance. Hazard ratios and their associated 95% confidence intervals will be estimated based on a Cox proportional hazards model with treatment and other factors as explanatory variables.

Kaplan-Meier estimates of the probability to experience a flare event will be calculated from the beginning of Treatment Period 2 along with 95% confidence intervals using Greenwood's formula. The cumulative probability to flare will be plotted against time.

The primary analysis will be based on the FAS for Treatment Period 2.

Specifically, a table of Survival analysis of time to flare in Treatment Period 2 will include randomized treatment, number of patients, number of events, Kaplan-Meier estimate of median of time to flare in days, Hazard ratio (95% Confidence interval) and p-value for the Stratified log-rank test. In addition, a figure of Kaplan-Meier estimates of the probability to flare by treatment in Treatment Period 2 will be drawn against days.

2.5.3 Handling of missing values/censoring/discontinuations

Missing data

All patients in Treatment Period 2 will have a value of time to flare either by having an event or being censored.

For the calculation of JIA ACR or flare, partially missing data for JIA ACR components will be imputed by Last Observation Carried Forward (LOCF).

Missing data for other variables will not be imputed. Observed data except JIA ACR components will be used in all analysis.

2.6 Analysis of secondary objectives

The analysis of secondary variables is descriptive only for FAS. Summary statistics will be presented. Summary statistics for continuous variables include N, mean, standard deviation, minimum, median, maximum, 25% and 75% quantiles, and number of patients with non-missing data. Baseline, post-baseline and absolute change will be presented for all summary statistics. Percent change from baseline will be presented for JIA ACR core components. For binary or discrete variables, the number of subjects in each category and relative frequencies will be provided.

The following secondary efficacy endpoints will be analyzed by visit for all patients and each JIA category by descriptive statistics in Treatment Period 1:

- JIA ACR 30/50/70/90/100
- Inactive disease status
- Each JIA ACR core component
- Change from baseline Juvenile Arthritis Disease Activity Score (JADAS) score
- Total enthesitis count
- Total dactylitis count

The following secondary efficacy endpoints will be analyzed by treatment and visit for all patients and each JIA category by descriptive statistics in Treatment Period 2:

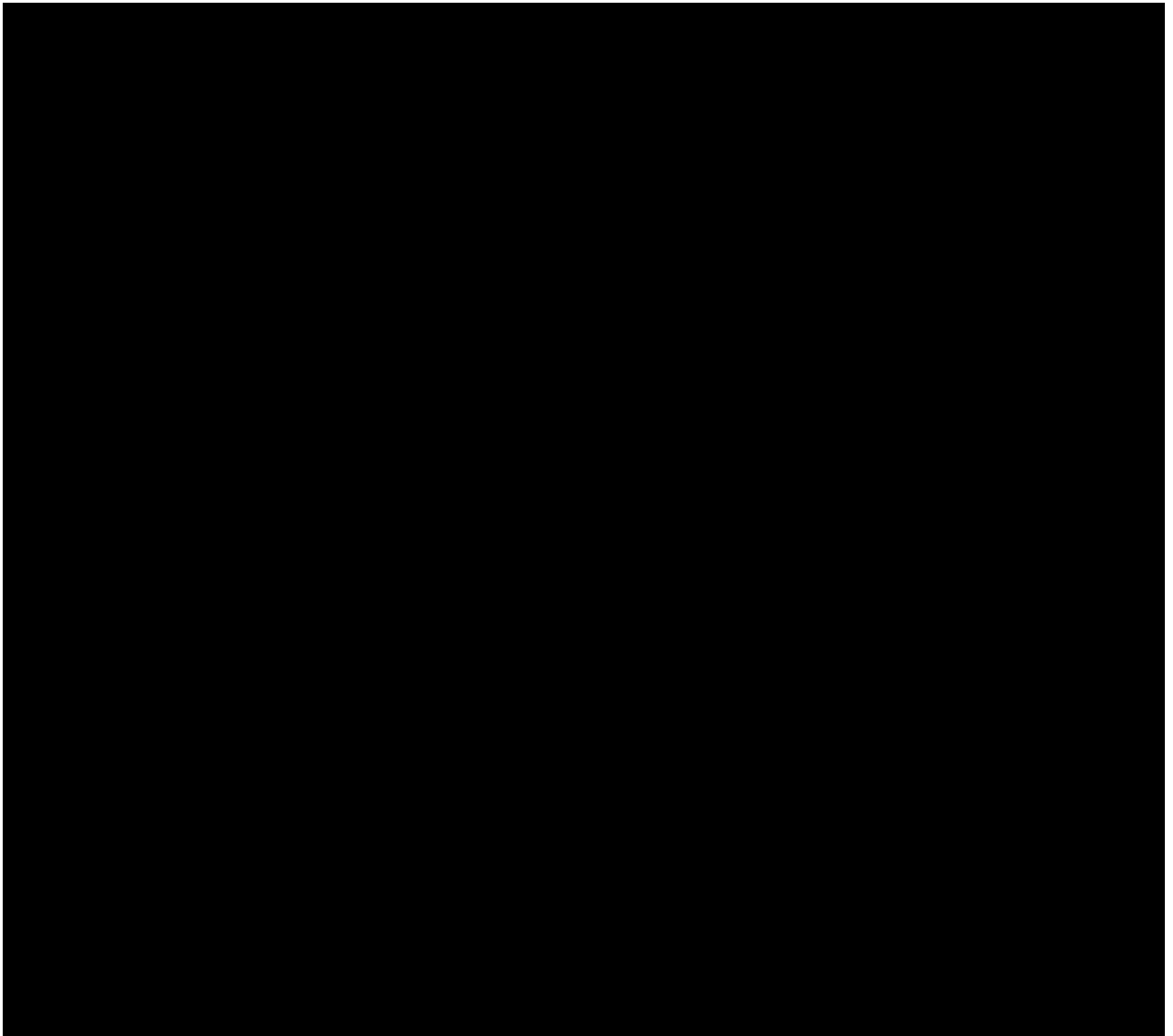
- JIA ACR 30/50/70/90/100
- Inactive disease status.

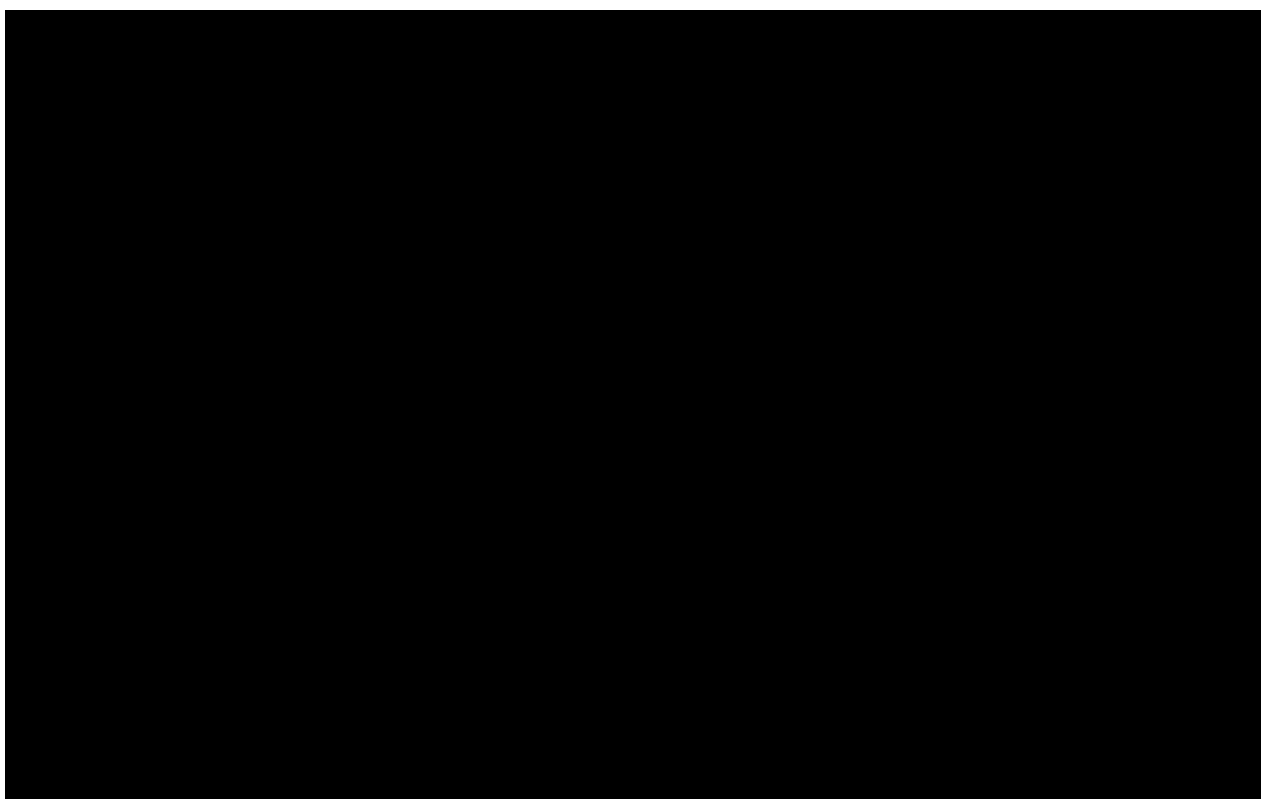
ACR pediatric response achieved in TP1 and TP2 will be summarized by descriptive statistics by treatment period, visit, and response criterion (30/50/70/90/100). ACR pediatric response

level achieved will also be plotted against visit for TP1. One figure (line graph) of JIA ACR 30/50/70/90/100 and inactive disease responses over all visits in Treatment Period 1 will be plotted.

A figure (bar chart) of JIA ACR 30/50/70/90/100 response and inactive disease at the end of Treatment period 2 will be plotted and the corresponding reference table will also be produced. The difference between treatment groups will be tested using the Cochran-Mantel-Haenszel (CMH) test, stratified by JIA category (ERA or JPsA) and another factor MTX use at baseline. Mean percent improvement from baseline to Week 12 will be plotted for JIA ACR core components other than CRP. For CRP, median percent change will be presented due to the outliers of CRP values.

JADAS-27 and JADAS-71 change from baseline will also be plotted against visit for TP1.





2.8 Safety analyses

The analysis of safety data by treatment may be provided for each Treatment Period separately and all periods combined, as appropriate. The analysis of safety data will be conducted on the Safety Set, which includes subjects who receive any study treatment. Safety analyses will be performed on treatment received or actual treatment as described below:

The actual treatment or treatment received for summaries of safety data will differ to the treatment assigned at randomization only if a subject received the wrong treatment during the entire treatment period.

The safety variables to be analyzed include Adverse events (AEs), clinical laboratory tests (hematology, chemistry and urinalysis), physical examination results, ECGs, and deaths. Safety variables are to be tabulated by descriptive statistics (n, mean, median, standard deviation, minimum, and maximum; or n and percent). No formal statistical testing is planned.

2.8.1 Adverse events (AEs)

The crude incidence of treatment emergent adverse events (TEAEs) (i.e. events started after the first dose of study treatment or events present prior to the first dose of study treatment but increased in severity based on preferred term and on or before last dose of study treatment + 84 days) will be summarized by primary system organ class and preferred term. Confidence intervals for the crude rate will be derived as described in [Section 5.2.3.1](#). In addition, exposure time-adjusted rates (incidence rate) including 95% confidence intervals by treatment will be provided for Treatment Period 2 (see [Section 5.2.4.1](#)) to adjust for differences in exposure.

Adverse events reported will be presented in descending frequency according to its incidence in secukinumab group starting from the most common event. Summaries (crude incidences only) will also be presented for AEs by severity and for study treatment related AEs. If a particular AE ‘severity’ is missing, this variable will be listed as missing and treated as missing in summaries. If a subject reported more than one adverse event with the same preferred term, the adverse event with the greatest severity will be presented. If a subject reported more than one adverse event within the same primary system organ class, the subject will be counted only once with the greatest severity at the system organ class level, where applicable.

Separate summaries will be provided for adverse events suspected to be related to study drug, deaths, serious adverse events, and adverse events leading to discontinuation and adverse events leading to temporary dose interruption.

Adverse events will also be reported separately by Standardized MedDRA Query (SMQ) according to MedDRA. The MedDRA version used for reporting the study will be described in a footnote.

Non-treatment emergent adverse events will be listed.

Algorithms for date imputations will be provided in Programming Dataset Specification (PDS).

For serious adverse events (SAEs) occurred during screening a listing will be prepared for all subjects screened including screening failures.

The safety analyses that will be performed for treatment emergent AEs and on treatment labs, ECG and vital signs for each analysis period is described in [Table 2-1](#).

Table 2-1 Overview of analyses on some safety endpoints

Analysis period	AEs & SAEs	AEs severity	by Study drug related AEs	AEs-SMQ	Risk	Notables for (vitals/ ECG), lab criteria
Treatment Period 1	•crude incidence	•crude incidence	•crude incidence	•crude incidence	•crude incidence	•crude incidence
Treatment Period 2	•crude incidence •	•crude incidence	•crude incidence	•crude incidence •	•crude incidence •	•crude incidence
Treatment Period 3	•crude incidence	•crude incidence	•crude incidence	•crude incidence	•crude incidence	•crude incidence
Entire treatment period (TEAEs)	•crude incidence •exposure adjusted incidence*	•crude incidence	•crude incidence	•crude incidence •exposure adjusted incidence*	•crude incidence •exposure adjusted incidence*	•crude incidence

*Exposure adjusted incidence rates will be done for the following:

- at the Primary SOC for AE analyses
- at the Primary SOC and Preferred Term (PT) for SAE analyses
- at the Level 1 and PT for Risks and SMQ analyses

Clinicaltrials.gov and EudraCT

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on treatment emergent adverse events which are not serious adverse events with an incidence greater than X% (0-5 %, as appropriate) and on treatment emergent serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE will be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

2.8.2 Laboratory data

The summary of lab data will only include on treatment data, which are defined as those lab assessments after the first dose of study treatment and on or before last dose + 84 days.

The summary of laboratory evaluations will be presented for three groups of laboratory tests (hematology, chemistry and urinalysis). In addition to the individual laboratory parameters the ratio "total cholesterol / HDL" will be derived and summarized.

For urinalysis, frequency tables will be presented.

Descriptive summary statistics for the change from baseline in Treatment Periods 1, 2 and 3 will be presented. These descriptive summaries will be presented by laboratory test and treatment group. Change from baseline will only be summarized for subjects with both baseline and post baseline values and will be calculated as:

$$\text{change from baseline} = \text{post baseline value} - \text{baseline value}$$

For each parameter, the maximum change (maximum decrease and maximum increase) from baseline, if appropriate for each study phase, will be analyzed analogously.

In addition, shift tables will be provided for all parameters to compare a subject's Week 12 laboratory evaluation relative to the most extreme laboratory test value within treatment period 2. For the shift tables, the normal laboratory ranges will be used to evaluate whether a particular laboratory test value was normal, low, high or "high and low" relative to whether or not the baseline value was normal, low, or high. These summaries will be presented by laboratory test and treatment group.

The following laboratory parameters will be analyzed with respect to numerical Common Terminology Criteria for Adverse Events (CTCAE) grades, given in [Table 2-2](#): hemoglobin (HGB), platelets, white blood cell count, neutrophils, lymphocytes, creatinine, total bilirubin (TBL), gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), glucose, cholesterol, triglycerides (TG).

These summaries will be split into hematology and chemistry for study level reports and the pooled summary of clinical safety (SCS).

Table 2-2 CTCAE grades for laboratory parameters to be analyzed

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4
HGB decreased (Anemia)	<LLN – 100 g/L	<100 – 80 g/L	<80 g/L	Life-threatening consequences; urgent intervention indicated
Platelet count decreased	<LLN – 75.0 x10e9 /L	<75.0 - 50.0 x10e9 /L	<50.0 – 25.0 x10e9 /L	<25.0 x 10e9 /L
White blood cell decreased	<LLN - 3.0 x 10e9 /L	<3.0 - 2.0 x 10e9 /L	<2.0 - 1.0 x 10e9 /L	<1.0 x 10e9 /L
Neutrophil count decreased	<LLN - 1.5 x 10e9 /L	<1.5 - 1.0 x 10e9 /L	<1.0 - 0.5 x 10e9 /L	<0.5 x 10e9 /L
Lymphocyte count decreased	<LLN - 0.8 x 10e9/L	<0.8 - 0.5 x 10e9 /L	<0.5 - 0.2 x 10e9 /L	<0.2 x 10e9 /L
Creatinine increased*	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 baseline; >3.0 - 6.0 x ULN	>6.0 x ULN
TBL increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN
GGT increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
ALT increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
AST increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
ALP increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Glucose increased (Hyperglycemia)	>ULN - 8.9 mmol/L	>8.9 - 13.9 mmol/L	>13.9 - 27.8 mmol/L	>27.8 mmol/L
Glucose decreased (Hypoglycemia)	<LLN - 3.0 mmol/L	<3.0 - 2.2 mmol/L	<2.2 - 1.7 mmol/L	<1.7 mmol/L
Cholesterol high	>ULN - 7.75 mmol/L	>7.75 - 10.34 mmol/L	>10.34 - 12.92 mmol/L	>12.92 mmol/L
Hypertriglyceridemia	1.71 - 3.42 mmol/L	>3.42 - 5.7mmol/L	>5.7 - 11.4 mmol/L	>11.4 mmol/L

*Note: for “creatinine increased” the baseline criteria do not apply

The number and percentage of subjects with newly occurring or worsening CTCAE grades after baseline evaluation will be presented for Treatment Periods 1, 2 and 3, and entire treatment period.

Shift tables will be presented comparing Week 12 laboratory result (CTCAE grade) with the worst results (expressed in CTCAE grade) during the treatment period 2 analyzed. Subjects with abnormal laboratory values will be listed and values outside the normal ranges will be flagged.

Summaries for newly occurring or worsening clinically notable lipid abnormalities will also be provided cumulatively for each of the following parameters and categories:

- HDL:
 - ≤LLN
 - <0.8 x LLN
- LDL, cholesterol, triglycerides:
 - ≥ULN
 - >1.5 x ULN
 - >2.5 x ULN

Newly occurring or worsening liver enzyme abnormalities will also be summarized based on the event criteria given in [Table 2-3](#):

Table 2-3 **Liver-related events**

Parameter	Criterion
ALT	>3xULN; >5xULN; >8xULN; >10xULN, >20xULN
AST	>3xULN; >5xULN; >8xULN >10xULN; >20xULN
ALT or AST	>3xULN; >5xULN; >8xULN >10xULN; >20xULN
TBL	>1.5xULN, >2xULN, >3xULN,
ALP	>2xULN, >3xULN, >5xULN
(ALT or AST) & TBL	ALT or AST >3xULN & TBL >2xULN; ALT or AST >5xULN & TBL >2xULN; ALT or AST >10xULN & TBL >2xULN
ALP & TBL	ALP >3xULN & TBL >2xULN ALP >5xULN & TBL >2xULN
(ALT or AST) & TBL & ALP	ALT or AST >3xULN & TBL >2xULN & ALP <2xULN (Hy's Law) Note: elevated ALP may suggest obstruction as a consequence of gall bladder or bile duct disease; ALP may also be increased in malignancy. FDA therefore terms Hy's Law cases as indicators of <i>pure hepatocellular injury</i> . This does not mean that cases of ALT or AST >3xULN & TBL >2xULN & ALP ≥2xULN may not result in severe DILI.

Notes:

1) In studies which enroll subjects with pre-existing liver disease, baseline LFT may be increased above ULN; in such a case it is meaningful to add the condition "and worse than baseline" to the abnormality criteria

For a combined criterion to be fulfilled, all conditions have to be fulfilled on the same visit. The criteria are not mutually exclusive, e.g. a subject with ALT = 6.42xULN is counted for ALT >3xULN and ALT >5x ULN.

Individual subject data listings will be provided for subjects with abnormal laboratory data. Data of subjects with newly occurring or worsening liver enzyme abnormalities will be listed in an additional listing.

In addition, three individual subject data listings will be provided for liver events, laboratory values and viral serology, autoimmunity, imaging, pathology, drug abuse for patients with liver events.

The laboratory values below Lower Level of Quantification (LLQ) or above Upper Level of Quantification (ULQ) will be imputed as LLQ or ULQ, respectively. The numerical part of the reported result will be treated as the actual LLQ or ULQ. These laboratory values will be displayed in listings using the standard unit with the reported sign ("<" or ">").

2.8.3 Vital signs

The summary of vital signs will only include on treatment data, which are defined as those vital sign measurements after the first dose of study treatment and on or before last dose + 84 days.

Analysis in vital sign measurement using descriptive summary statistics for the change from baseline for each post-baseline visit will be performed. These descriptive summaries will be

presented by vital sign and treatment group. Change from baseline will only be summarized for subjects with both baseline and post-baseline values and will be calculated as:

$$\text{change from baseline} = \text{post-baseline value} - \text{baseline value}$$

The number and percentage of subjects with newly occurring notable vital signs will be presented. Criteria for notable vital sign abnormalities are as follows.

Note: The age is the age at the time of the visit. It will be derived as follows:

Integer part of ((assessment date – imputed birth date) / 365.25)

Systolic blood pressure (mmHg):

- High: >ULN and Increased >20 in change from baseline

Diastolic blood pressure (mmHg):

- High: >ULN and Increased >20 in change from baseline

Pulse (bpm):

- High: >ULN and Increased >20 in change from baseline
- Low: <LLN and Decreased >20 in change from baseline

Note: Only post-baseline values will be flagged as notable abnormalities

Table 2-4 **Criteria for normal vital sign for pediatric patients**

Age group	Systolic BP(mmHg)	Diastolic BP(mmHg)	Pulse (bpm)
2-5 years	76-120	45-80	55-120
6 -11 years	90-130	50-80	50-105
12-17 years	90-145	55-90	45-95
18 years and over	90-140	60-90	60-100

2.8.4 Immunogenicity

A listing of immunogenicity (anti-AIN457 antibodies) will be provided. Also, an overview of subjects with anti-drug antibodies will be summarized.

2.8.5 Compound specific safety evaluation

Safety topics of interest, such as risks defined in the Risk Management Plan (RMP) or topics of interest regarding signal detection or routine analysis are defined in the Program Case Retrieval Sheet that is stored in Global Programming and Statistics Environment (GPS).

The crude incidence and exposure-adjusted incidence rates for RMP risks will be summarized. In addition, listings will be provided presenting which subjects experienced which risk.

Important note: For the evaluation of risks primary and secondary system organ classes of the MedDRA dictionary will be considered.

2.9 Pharmacokinetic endpoints

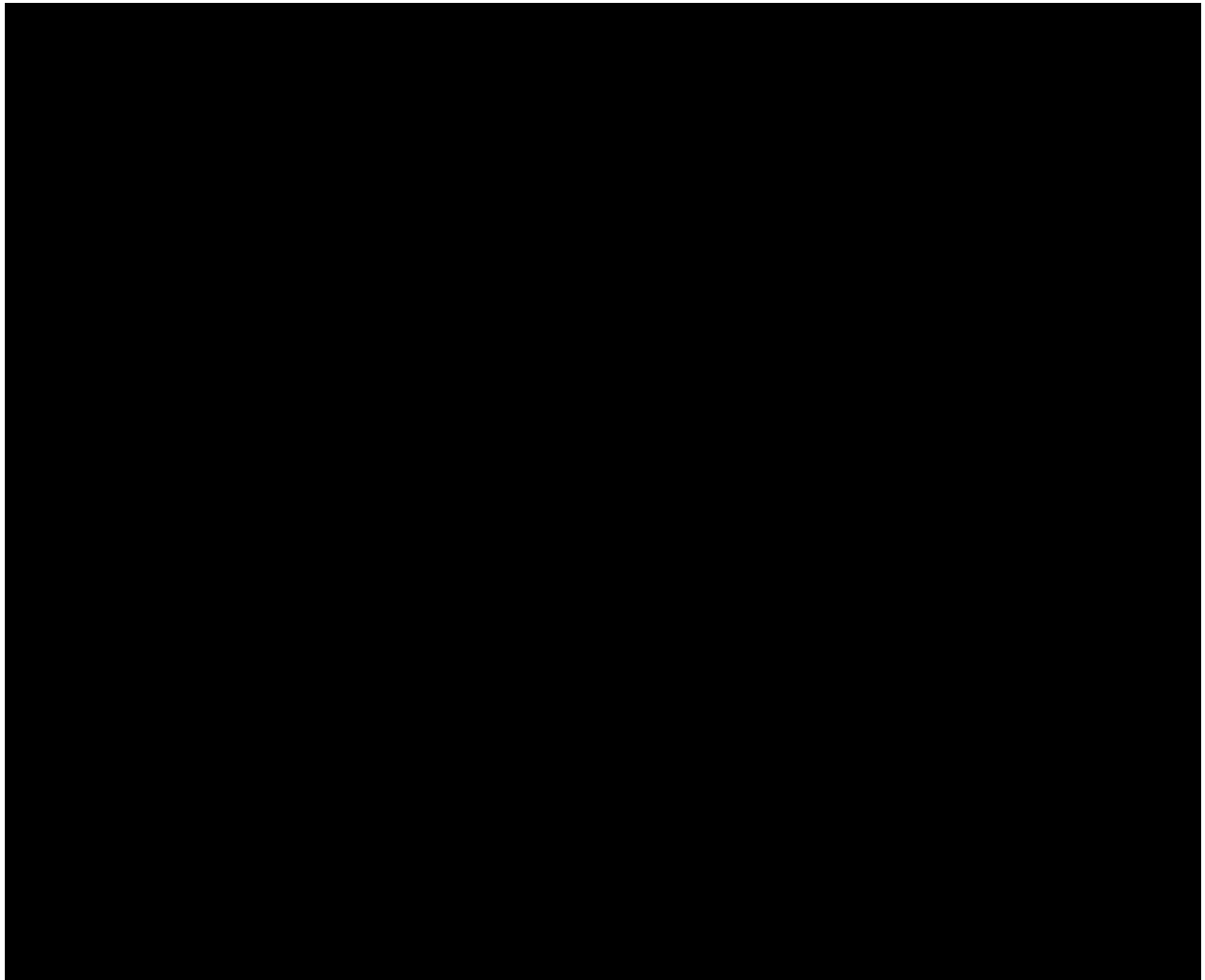
The following PK parameters will be determined: C_{min} , C_{ss} . All completed subjects with quantifiable pharmacokinetic (PK) measurements of secukinumab will be included in the

pharmacokinetic data analysis. Serum concentrations will be expressed in mass per volume units. All concentrations below the limit of quantification as well as missing data will be labeled as such in the concentration data listings. PK concentrations will be summarized by Treatment Period, visit and treatment group. In addition to mean, standard deviation (SD), coefficient of variation (CV), median and quartiles, the geometric mean and geometric coefficient of variation (CV) and n(log) will be presented. The formula for deriving the geometric mean and CV (%) is as following:

- $CV (\%) = (SD/mean) * 100$,
- $geometric\ mean = \exp((\text{sum of log transformed data}) / \text{number of non-missing data points after log transformation})$,
- $geometric\ CV = \sqrt{\exp(\text{variance of log-transformed data}) - 1} * 100$.

In addition, sample number, concentration, sample date, sample time at pre-dose and minutes pre-dose and elapsed time from first dose (in days) will be listed by treatment group.

Values below lower limit of quantification/below detection limit will be imputed by 0.



2.11.2 Efficacy Evaluation

2.11.2.1 Description of efficacy variables

JIA ACR response criteria

Standard ACR pediatric Criteria (JIA ACR criteria) consist of 6 core components which will be assessed as scheduled in Table 6-1 of the protocol. JIA ACR 30/50/70/90/100 are defined as 30%, 50%, 70%, 90% and 100% improvement from baseline respectively in a minimum of three variables in the core set with no more than one variable worsening more than 30% as defined in the ACR criteria.

The 6 core set variables are summarized below:

- Physician global assessment of disease activity on a 0 - 100 mm VAS from 0 mm = no disease activity to 100 mm = very severe disease activity
- Parent or patient's (if appropriate in age) Global Assessment of Subject's overall well-being on a 0-100 mm VAS from 0 mm = very well to 100 mm = very poor.
- Functional ability: Childhood Health Assessment Questionnaire (CHAQ[®])
 - Within each of the 8 categories only the item indicating the most severe impairment will contribute to the category score (3 is the most severe, (Without any difficulty) = 0, (With some difficulty) = 1, (With much difficulty) = 2, (Unable to do) = 3).
 - If the patient indicates the need for an assistance from another person, or the use of an aid/device to perform a task, then the minimum score for the category is 2.
 - The score is set to 2 also if (Not Applicable) is chosen and the patient indicates the need for an assistance from another person or the use of an aid/device to perform a task.
 - CHAQ disability score has 8 category scores. The highest score for component questions within each category determines the score for that category and the final score is obtained by the average of the 8 category scores. (i.e. the range for CHAQ score is (0, 3)). CHAQ is set to missing if patients didn't have the scores for all 8 categories.
- Number of active joints using the ACR definition (The ACR definition of active arthritis is any joint with swelling or in the absence of swelling, limitation of motion accompanied by either pain on motion or tenderness not due to deformity), so three types of data will be collected and used for deriving number of active joints: Swelling, Pain, and Limitation of motion.
- Number of joints with limited range of motion
- Laboratory measure of inflammation: CRP (mg/L)
 - CRP local lab value will be standardized according to [Appendix 5.3](#).

Note for CRP variable: in case at the Baseline visit the CRP is within the normal limit, then improvement or worsening in this variable that remains within the normal range at the study visit for which response is being calculated cannot contribute as one of the 6 parameters of either improvement or worsening.

The respective response variables listed above will be used by [REDACTED] to determine ACR Pediatric response, responder status at Week 12, and flare occurrence in Treatment Period 2. These results will be

communicated to the investigator prior to the patient leaving the study site. Additionally, these components will be used to determine JADAS and inactive disease status ([Wallace et al. 2011](#)) as part of secondary [REDACTED] analyses.

ACR definition of flare for JIA

Both criteria 1 and 2 must be fulfilled to meet the definition of a disease flare. Criteria changes described are relative to the End of Treatment Period 1 (Week 12 visit).

1. $\geq 30\%$ worsening in at least 3 of the 6 ACR response variables
 - Physician global assessment of overall disease activity
 - Parent or patient global assessment of overall well-being
 - Functional ability (CHAQ[®])
 - Number of joints with active arthritis
 - Number of joints with limited range of motion
 - Index of inflammation: CRP
2. $\geq 30\%$ improvement in no more than 1 of the 6 ACR response variables

Contingencies:

- if the Physician or Parent Global Assessment is one of the 3 response variables used to define flare, then worsening of ≥ 20 mm (1-100mm visual analogue scale) must be present
- if the number of active joints or joints with limitation of motion is one of the 3 response variables used to define flare, then worsening in ≥ 2 joints must be present
- if CRP is used to define flare, then CRP must be >10 mg/L

Note for CRP: in case at Week 12 visit the CRP is within the normal limit, then worsening in the value at the study visit for which flare is being calculated must be above the upper limit of normal and at least 30% higher than the Week12 visit value to count as worsening in that parameter for the definition of flare. CRP must change from normal to abnormal or from abnormal to a higher value in order to be considered for the Flare.

ACR Components

Tender joint count and swollen joint count

The number of joints with active arthritis at each visit will be determined by applying the ACR definition to the number of joints with swelling, tenderness and limited range of motion at each scheduled visit for all patients throughout the study. The ACR definition of active arthritis is any joint with swelling or, in the absence of swelling, limitation of motion accompanied by either pain on motion or tenderness not due to deformity. The active joint count will therefore range from 0 to 73.

Tender 75 joint count (TJC)

The following 75 joints will be scored as either tender or not tender:

- Temporomandibular joints: 2
- Sternoclavicular joints: 2
- Acromioclavicular joints: 2
- Shoulders: 2
- Elbows: 2
- Wrists: 2
- Hands:
 - distal interphalangeal
 - 10 proximal interphalangeal
 - 10 metacarpophalangeal
- Hip: 2
- Knee: 2
- Ankle: 2
- Subtalar joints: 2
- Intertarsal joints: 2
- Feet:
 - 10 metatarsophalangeal joints
 - 10 toes
- Cervical spine is assessed as a single joint
- Thoracic spine is assessed as a single joint
- Lumbar spine is assessed as a single joint
- Sacroiliac joints: 2

Joint tenderness is to be scored as present or absent. For there to be consistency between the joint assessments, it is strongly recommended that the same evaluator perform these assessments at all visits.

Swollen joint count (SJC)

A total of 68 joints are to be scored as either swollen or not swollen. The same 75 joints assessed for tenderness will also be assessed for swelling excluding the cervical spine, thoracic spine, lumbar spine, 2 hips and 2 sacroiliac joints.

For there to be consistency between the joint assessments, it is strongly recommended that the same evaluator perform these assessments at all visits.

Joint counts with limitation of motion

A total of 69 joints will be assessed for limitation of motion at each scheduled visit for all patients throughout the study. The same 75 joints assessed for tenderness (see Section 6.4.8 of

the protocol) will also be assessed for limitation of motion excluding the 2 sternoclavicular, 2 acromioclavicular joints as well as the 2 sacroiliac joints.

Parent's/patient's Global Assessment of subject's overall well-being (VAS)

The parent's or patient's global assessment of the patient's overall well-being will be assessed on the VAS that is part of the CHAQ[®]. The VAS scale ranges from 0-100 mm, from very well (0 mm) to very poor (100 mm).

Scores on the 100 mm linear scale will be measured to the nearest millimeter from the left.

Physician's global assessment of PsA disease activity

The physician will rate the patient's current condition on a 0-100 mm VAS (see Appendix 5 of the protocol), ranging from no disease activity (0 mm) to very severe disease activity (100 mm), at each scheduled visit for all patients throughout the study.

Scores on the 100 mm linear scale will be measured to the nearest millimeter from the left. To enhance objectivity, the physician must not be aware of the specific parent's or patient's global assessment of patient's overall well-being, when performing his own assessment on that patient.

Childhood Health Assessment Questionnaire (CHAQ[®])

The Childhood Health Assessment Questionnaire, CHAQ[®] (see Appendix 6 of the protocol), will be used to assess physical ability and functional status of patients as well as quality of life. The disability dimension consists of multiple choice and VAS items concerning difficulty in performing eight common activities of daily living; dressing and grooming, arising, eating, walking, reaching, personal hygiene, gripping and activities. Subjects choose from four response categories, ranging from 'without any difficulty' to 'unable to do'.

This questionnaire should be completed by the parent (or, for patients 18 years and older, the questionnaire will be completed together by both the patient and parent) according to schedule in Table 6-1 of the protocol. The CHAQ[®] will be completed only in a validated version of the instrument in the language understandable to the parent and/or patient.

C-reactive protein (CRP)

Blood for this assessment will be obtained in order to identify the presence of inflammation, to determine its severity, and to monitor response to treatment.

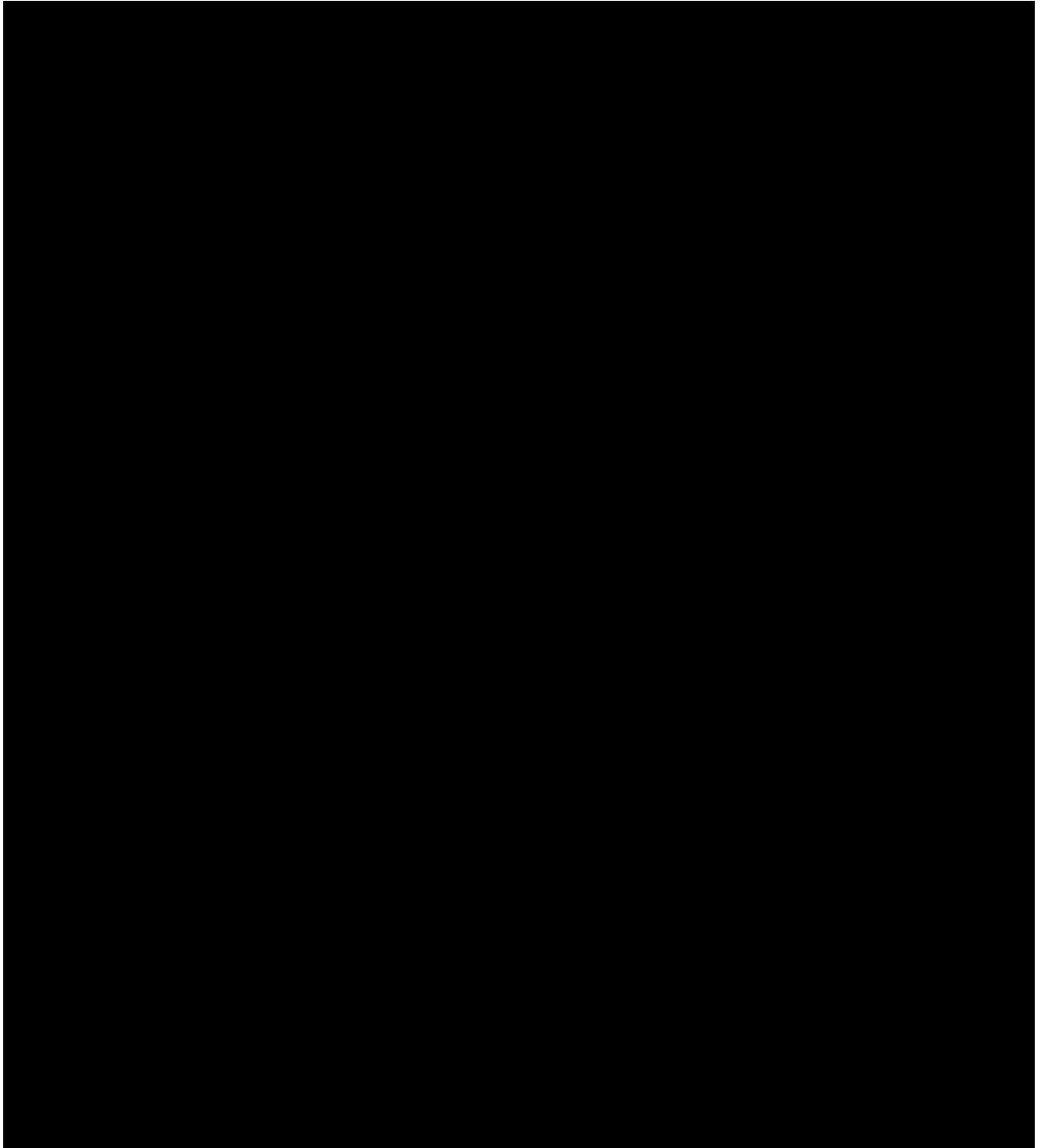
Total dactylitis count

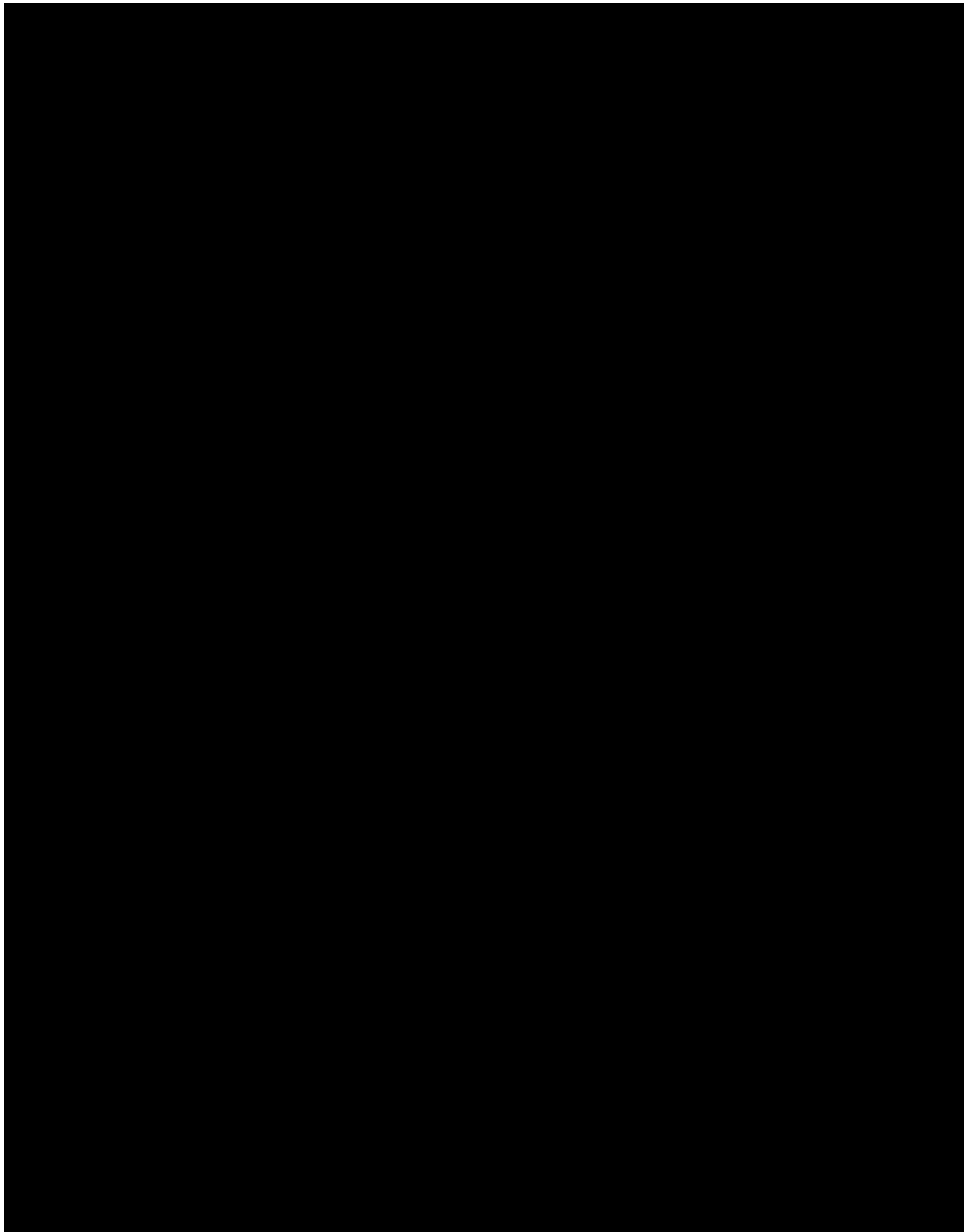
The dactylitis count is the number of fingers and toes presenting with dactylitis, with a range of 0-20.

Total enthesitis count

The following 16 enthesal sites will be assessed for the presence or absence of tenderness (enthesitis) on each side of the body:

- Anterior Entheses: Greater trochanter of the Femur; Medial condyle of the femur; Lateral condyle of the femur
- Posterior Entheses: Greater tuberosity of humerus; medial epicondyle of humerus; lateral epicondyle of humerus, Achilles tendon; and calcaneal insertion of the plantar fascia.





Juvenile Arthritis Disease Activity Score (JADAS)

The Juvenile Arthritis Disease Activity Score (JADAS) is a composite disease activity score developed and validated for juvenile idiopathic arthritis (JIA). JADAS consists of four components: physician global assessment of disease activity on a 10 cm VAS (0=no activity, 10=maximum activity); parent/patient global assessment of well-being on a 10 cm VAS (0=very well, 10=very poor); number of joints with active disease; and an inflammatory marker (ESR) ([Consolaro, 2009](#)).

The JADAS-27 includes the following joints: cervical spine, elbows, wrists, metacarpophalangeal joints (MCP) (from first to third), proximal interphalangeal (PIP) joints, hips, knees, and ankles.

The JADAS-71 includes the following joints: cervical spine, temporomandibular, sternoclavicular, acromioclavicular, shoulder, elbow, wrist, MCP, PIP, Distal interphalangeal, hip, knee, ankle, subtalar, tarsometatarsal – *replaced by intertarsal in our study*, metatarsophalangeal, foot interphalangeal.

The JADAS is calculated as the simple linear sum of the scores of its 4 components, which yields a global score of 0–57, 0–101 for the JADAS-27 and JADAS-71 respectively.

JADAS-CRP is adapted by substituting ESR with CRP as the inflammatory marker (Nordal 2012). CRP is truncated to a 0–10 scale according to the following formula: $(\text{CRP (mg/l)} - 10)/10$, similar to the truncated ESR used in JADAS. Before calculation, CRP values <10 mg/l will be converted to 10 and CRP values >110 mg/l will be converted to 110.

The following formula to calculate the JADAS27 using CRP (mg/L) will be used:

$\text{JADAS27-CRP} = (27 \text{ AJC})^* + \text{Physician Global Assessment of Disease Activity (0-10cm)} + \text{Parent's or Patient's Global Assessment of Patient's overall well-being (0-10cm)} + \text{CRP (standardized in mg/dl unit (=CRP/10))}$.

27 AJC=Active joints count based on 27 joints list (see Table 2-7 below)

The following formula to calculate the JADAS71 using CRP (mg/L) will be used:

$\text{JADAS71-CRP} = (71 \text{ AJC})^* + \text{Physician Global Assessment of Disease Activity (0-10cm)} + \text{Parent's or Patient's Global Assessment of Patient's overall well-being (0-10cm)} + \text{CRP (standardized in mg/dl unit (=CRP/10))}$.

71 AJC=Active joints count based on 71 joints list (see Table 2-7 below)

The corresponding score will be calculated only when all components are available.

Table 2-7 Joints Identification for Disease Activity Scores and Indexes

*Table: Joints index

	In CRF	Side	71-joint	27-joint
Cervical spine	Yes		+	+
Temporomandibular	Yes	R/L	+	–
Sternoclavicular	Yes	R/L	+	–
Acromioclavicular	Yes	R/L	+	–
Shoulder	Yes	R/L	+	–
Elbow	Yes	R/L	+	+
Wrist	Yes	R/L	+	+
Metacarpophalangeal (MCP)				
1	Yes	R/L	+	+
2	Yes	R/L	+	+
3	Yes	R/L	+	+
4	Yes	R/L	+	–
5	Yes	R/L	+	–
Proximal interphalangeal (PIP)				
1	Yes	R/L	+	+
2	Yes	R/L	+	+
3	Yes	R/L	+	+
4	Yes	R/L	+	+
5	Yes	R/L	+	+
Distal interphalangeal				
2	Yes	R/L	+	–
3	Yes	R/L	+	–

		In CRF	Side	71-joint	27-joint
	4	Yes	R/L	+	–
	5	Yes	R/L	+	–
Hip		Yes	R/L	+	+
Knee		Yes	R/L	+	+
Ankle		Yes	R/L	+	+
Subtalar		Yes	R/L	+	–
Tarsometatarsal		INTERTARSAL	R/L	+	–
Metatarsophalangeal					
	1	Yes	R/L	+	–
	2	Yes	R/L	+	–
	3	Yes	R/L	+	–
	4	Yes	R/L	+	–
	5	Yes	R/L	+	–
Foot interphalangeal (Toe)					
	1	Yes	R/L	+	–
	2	Yes	R/L	+	–
	3	Yes	R/L	+	–
	4	Yes	R/L	+	–
	5	Yes	R/L	+	–

Inactive Disease status

Clinical inactive disease definition is adapted from the ACR criteria of [Wallace et al 2011](#). All must be met:

- No joints with active arthritis
- No uveitis
- CRP value within normal limits for the laboratory where tested or, if elevated, not attributable to JIA
- Physician's global assessment of disease activity score ≤ 10 mm
- Duration of morning stiffness attributable to JIA ≤ 15 min

2.12 Interim analysis

No interim analysis will be performed, see section 4 'Change to protocol specified analysis' for details. [REDACTED] will perform on behalf of Novartis final analysis when the study is completed.

2.13 Summary of statistical analysis

Table 2-8 is a summary of efficacy analysis in this study by treatment period and statistical method used.

Table 2-8 Summary of efficacy analysis by treatment period and statistical method

	TP1	TP2	TP3	Entire treatment period (overall)/across period	Statistical Method: descriptive statistics?
Treatment group	AIN	AIN, placebo	AIN, placebo, total	AIN, placebo	
Disposition/ Number (%) of patients in the analysis sets	X	X	X	Screening period and overall	Y
Demographics and background characteristics at baseline	X	X			Y
exposure to study drug	X	X	X	X	Y

	TP1	TP2	TP3	Entire treatment period (overall)/across period	Statistical Method: descriptive statistics?
Prior medications	X				
Concomitant medications	X	X	X	X	Y
Time to flare		X			Survival analysis
JIA ACR 30/50/70/90/100	X	X	Only one figure and one table for subjects who flared on TP2, which combine all ACR pediatric responses (JIA ACR 30/50/70/90/100)	Only one table and one figure for all subjects randomized to AIN457 group in TP2 for overall study, which combine all ACR pediatric responses (JIA ACR 30/50/70/90/100)	Y
Inactive disease status	X	X			Y
JIA ACR core component	X	X			Y
Change from baseline in JADAS score	X	X			Y
Total enthesitis count	X	X			Y
Total dactylitis count	X	X			Y

	TP1	TP2	TP3	Entire treatment period (overall)/across period	Statistical Method: descriptive statistics?
<div></div> JADAS, VAS and CHAQ				Period 2 and the end of study	
PK	X	X	X		Y

Table 2-9 Summary of Safety analysis by treatment period and statistical method

	TP1	TP2	TP3	Entire treatment period (overall)/across period	Statistical Method: descriptive statistics?
Treatment group	AIN	AIN, placebo	AIN, placebo, total	AIN: TP1+TP2, TP1+TP2+TP3 TP1+TP3, TP1 Any subject taking only AIN Placebo: TP1+TP2, TP1+TP2+TP3 Any subject taking placebo at any time total	
Hematology: Change from baseline by parameter, visit and treatment	X	X	X	X	Y
Clinical Blood chemistry: Change from baseline by parameter, visit and treatment	X	X	X	X	Y
Hematology: Notable abnormality newly occurring by treatment	X	X	X	X	Y
Chemistry: Notable abnormality newly occurring by treatment	X	X	X	X	Y
Hematology: Shift table from week 12 in part 2 by parameter and treatment		X			Y
Chemistry: Shift table from week 12 in part 2 by parameter and treatment		X			Y

	TP1	TP2	TP3	Entire treatment period (overall)/across period	Statistical Method: descriptive statistics?
Vital signs/weight: Change from baseline by parameter, treatment and visit	X	X	X	X	Y
Vital signs: Notable abnormality newly occurring by parameter and treatment	X	X	X	X	Y
ECG: Changes from baseline by treatment	week 12	week 52	week 104	X	Y
Adverse events by primary system organ class, preferred term and treatment	X	X	X	X	Y
Adverse events by primary system organ class, preferred term, maximum severity and treatment	X	X	X	X	Y
Serious adverse events by primary system organ class, preferred term and treatment	X	X	X	X	Y
Adverse events causing study drug discontinuation by primary system organ class, preferred term and treatment	X	X	X	X	Y
Deaths by primary system organ class,	X	X	X	X	Y

	TP1	TP2	TP3	Entire treatment period (overall)/across period	Statistical Method: descriptive statistics?
preferred term and treatment					

3 Sample size calculation

It is assumed that the Flare-free time follows an exponential distribution with a constant hazard ratio.

The hazard ratio of flare events for the secukinumab group relative to placebo group is estimated to be 0.32 in Treatment Period 2. The hazard ratio of 0.32 was used to establish the sample size necessary in Treatment Period 2 and consequently Treatment Period 1 (derived from the median time to disease flare for ETANERCEPT and placebo in [Lovell et. al. 2000](#)). With the hazard ratio assumed to be 0.32, 33 flares are necessary to detect a statistically significant difference between secukinumab and placebo assuming 90% power and a 1-sided significance level of 0.025. No data is available to estimate the placebo hazard rate beyond 6-months. Given that uncertainty and a maximum 21-month follow-up in Treatment Period 2, the total sample size necessary to achieve 33 flares in Treatment Period 2 is estimated to be at least 60 and at most 80 patients. Assuming approximately 70% to 85% of patients respond in Treatment Period 1, the estimated minimum number of patients treated in Treatment Period 1 is between 70 and 86. Under the assumption of 12 months of accrual duration, the total maximum expected study duration is 33 months. The expected number of flare events is 12 and 21 respectively for secukinumab and placebo group in Treatment Period 2.

4 Change to protocol specified analyses

[REDACTED]

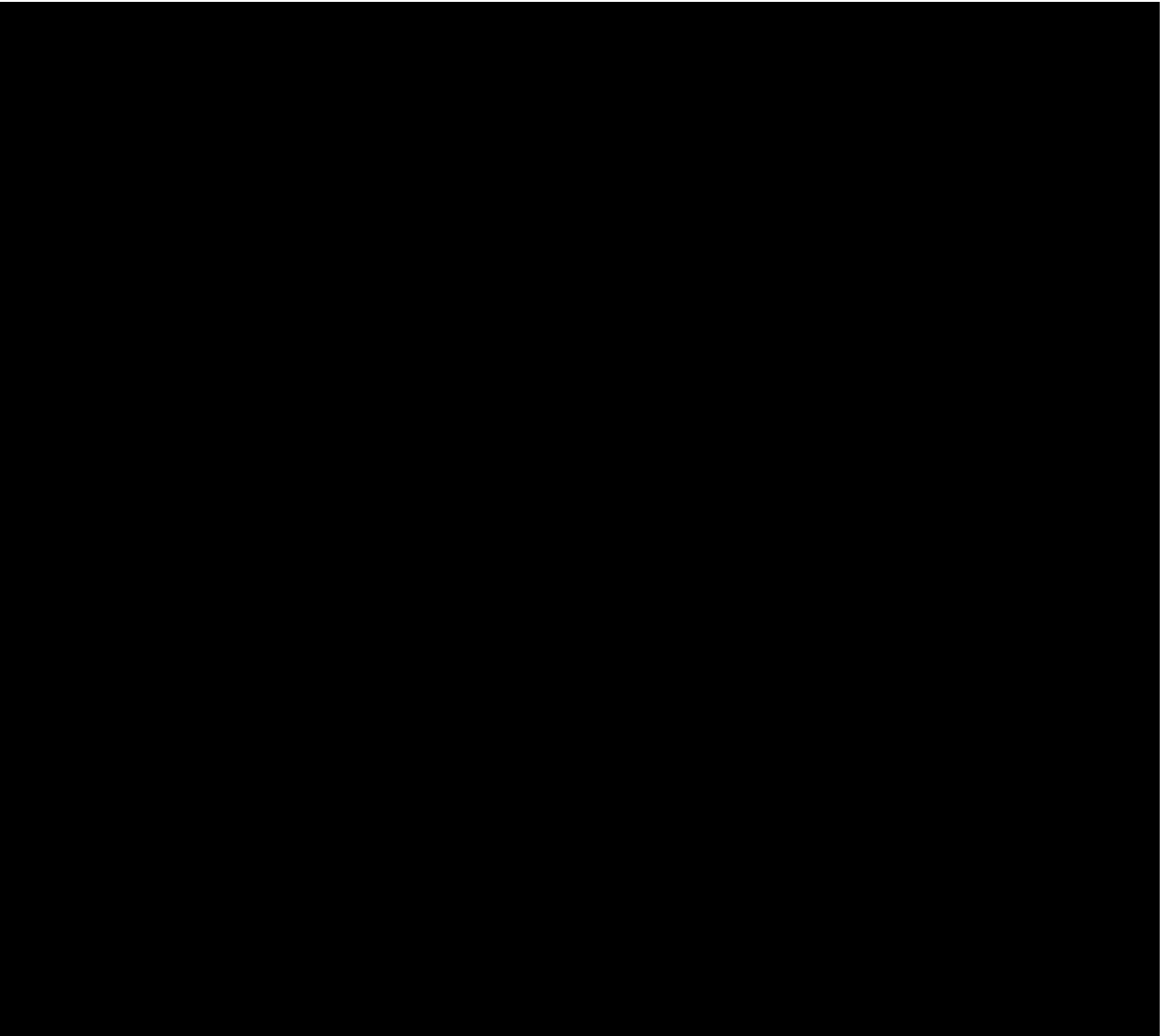
Prior and concomitant therapies will be reported based on the Safety Set (instead of FAS specified in the protocol), since Safety Set is the standard analysis set for reporting prior and concomitant therapies.

Vital signs criteria for notable abnormalities in Table 2-4 was updated as per AIN457 program level update, based on previous DMC feedback.

[REDACTED]

5 Appendix

5.1 Visit Windows



For early discontinuation visits in the CRF, it states either “week 12” (for discontinuation in period 1) or “week 104” (for discontinuation in period 2 or 3) instead of the actual study week, so the early discontinuation visit will be re-mapped to the next scheduled assessment week based on the patients available visit. Different parameters have different assessment schedules, so the early discontinuation visit will be re-mapped for different parameters according to each parameter’s assessment schedule. The follow-up visit “week 112” will be analyzed as follow-up and not re-mapped to any study week.

5.2 Statistical methodology and assumptions

5.2.1 Analysis of continuous data

5.2.1.1 Summary statistics for continuous data

Summary statistics (including N, mean, standard deviation, minimum, lower quartile, median, upper quartile, maximum) will be provided for continuous data by study treatment period, visit and treatment group.

Minimum and maximum will be presented to the same number of decimal places as the raw data, mean, median to one additional decimal place, and standard deviation to two additional decimal places.

5.2.1.2 Kaplan-Meier analysis

The SAS procedure PROC LIFETEST is used to obtain Kaplan-Meier estimates of the proportion of patients with disease flare.

- The Kaplan-Meier estimate for the cumulative flare-free rate along with the corresponding 95% confidence interval, using Greenwood's formula to compute the estimate of the standard error, at specific time points,
- median (95% confidence interval) and the estimate of the event rate at the end of the Treatment Period 2 will be provided.

The SAS procedure PROC LIFETEST will be used to obtain Kaplan-Meier estimates of the time to event variables.

The Kaplan-Meier estimate will be derived along with the corresponding 95% confidence interval, using Greenwood's formula to compute the estimate and the standard error, at specific time points,

The format of the SAS code is as follows:

```
proc lifetest data=<input_dataset> method=km outsurv=<output_dataset> reduceout  
timelist=(1 to xxx by 28) timelist=(28 to xxx by 28);  
strata <treatment>;  
time <time variable>*<censor variable>(1);  
run;
```

Explanations of the variables used and some SAS options:

- The time variable contains the calculated time to event values (time to last efficacy evaluation (i.e. flare=no evaluation in TP2) for lack of efficacy).
- For the censoring variable, the value 1 indicates censoring. That is, the values of the time variable are considered censored if the corresponding values of the censoring variable are 1; otherwise, if the censoring variable equals 0, they are considered as event times.

SAS OUTPUT DATASET:

- outsurv; contains the product-limit survival estimates (from which the cumulative event rates will be extracted by taking Estimated Survival Function if necessary). Additionally, 95% confidence intervals based on Greenwood's formula will be provided.

Stratified log-rank test

Log-rank tests will be computed, adjusted for the stratification variable of JIA category, and another factor MTX use at baseline. The test statistics are computed by pooling the statistics for treatment over the strata.

```
proc lifetest data=<input_dataset> method=km notable;  
  strata < var> / group=<treatment>;  
  time <time variable>*<sensor variable>(1);  
run;
```

The p-value obtained by fitting this model is two-sided. In order to obtain the one-sided p-value, the p-value obtained by the SAS procedure above will be divided by two, provided that the estimated effect is in the hypothesized direction. If the estimated effect is in the other direction, then the p-value will be calculated as $1 - [\text{p-value}/2]$.

5.2.1.3 Cox's proportional hazards model

Differences between treatment groups in time to event variables will be analyzed using Cox's proportional hazards regression model with treatment group and stratification factor (JIA categories (ERA and JPsA) and another factor MTX use at baseline (Yes/No)) as explanatory variables. Hazard ratios and their associated 95% confidence intervals will be estimated. This analysis will be performed using SAS PROC PHREG with options of TIES=BRESLOW (which is the default) and RISKLIMITS. The format of the SAS code is as follows:

```
proc phreg data=<input_dataset>;  
  model <time variable>*<sensor>(1)=<treatment> <covariates> /  
  ties=breslow rl;  
run;
```

The hazard ratio and its corresponding 95% confidence interval will be computed using the above model. The p-value obtained by fitting this model is two-sided. In order to obtain the one-sided p-value, the p-value obtained by the SAS procedure above will be divided by two, provided that the estimated effect is in the hypothesized direction. If the estimated effect is in the other direction the p-value is calculated as $1 - [\text{p-value}/2]$.

Univariate models and a multivariate model are fitted to explore the effect on time to flare of treatment, of the stratification variables (JIA category) and another factor MTX use at baseline. The format of the SAS code is as follows:

```
proc phreg data=<input_dataset>;  
  model <time variable>*<cursor>(1)=<explanatory variable(s)> /  
  ties=breslow rl;  
run;
```

The proportionality of the hazard function will be tested in all the univariate models and in the final multivariate model (cf. below “Checking of model assumptions”).

Checking of model assumptions

The assumption of proportionality of the hazard function(s) over time will be tested using a Cox proportional hazards regression model which includes treatment and a time-dependent explanatory variable created through the interaction between the response variable (time to event) and treatment:

```
proc phreg data=<input_dataset>;  
  model <time variable>*<cursor>(1)=<treatment> <covariates> treat_time  
    <covariate1_time, ...>;  
  treat_time = <treatment>*log(<time variable>);  
  <covariate1_time> = <covariate1>*log(<time variable>);  
  <covariate2_time> = <covariate2>*log(<time variable>);  
  /* add interaction terms for all covariates in the model */  
  proportionality_test: test treat_time, <covariate1_time>,  
    <covariate2_time>;  
run;
```

In addition, a graphical method will be used for checking the proportional hazards assumption. A plot of log-log survivor function versus time for each of the treatments will be used, using PROC LIFETEST as described in section Kaplan-Meier analysis, above. Approximate parallelism between the curves for the treatment groups would have provided supportive evidence of the proportional hazards assumption.

5.2.2 Analysis of binary (and categorical) data

5.2.2.1 Summary statistics for binary and categorical data

Summary statistics for discrete variables will be presented in contingency tables and will include count and frequency in each category. If applicable, confidence intervals will be derived as well based on the score method including continuity correction [[Newcombe \(1998\)](#)]:

With z as $(1-\alpha/2)$ -quantile of the standard normal distribution (SAS: $z=\text{PROBIT}(1-\alpha/2)$), n as total number of subjects (i.e. number of subjects in the denominator), and p as estimated crude incidence (number of subjects with event / n) it is $q=1-p$

Then the lower limit is

$$L = \max \left(0, \frac{2np + z^2 - 1 - z\sqrt{z^2 - 2 - \frac{1}{n} + 4p(nq + 1)}}{2(n + z^2)} \right)$$

and the upper limit is

$$U = \min \left(1, \frac{2np + z^2 + 1 + z\sqrt{z^2 + 2 - \frac{1}{n} + 4p(nq - 1)}}{2(n + z^2)} \right).$$

In addition, if $L > p$ then $L = p$ and if $U < p$ then $U = p$.

5.2.3 Crude incidence estimates

5.2.3.1 Crude incidence and 100*(1- α)% confidence interval

For n subjects, each at risk to experience a certain event with probability π , the crude incidence is estimated as $p=x/n$, where x is the number of subjects with the event.

Absolute and relative frequencies will be displayed as well as 95% confidence interval for the relative frequency based on the score method including continuity correction [[Newcombe \(1998\)](#)].

With z as $(1-\alpha/2)$ -quantile of the standard normal distribution (SAS: $z=\text{PROBIT}(1-\alpha/2)$), n as total number of subjects (i.e. number of subjects in the denominator), and p as estimated crude incidence (number of subjects with event / n) it is $q=1-p$.

Then the lower limit is

$$L = \max \left(0, \frac{2np + z^2 - 1 - z\sqrt{z^2 - 2 - \frac{1}{n} + 4p(nq + 1)}}{2(n + z^2)} \right)$$

and the upper limit is

$$U = \min \left(1, \frac{2np + z^2 + 1 + z \sqrt{z^2 + 2 - \frac{1}{n} + 4p(nq - 1)}}{2(n + z^2)} \right).$$

In addition, if $L > p$ then $L = p$ and if $U < p$ then $U = p$.

5.2.4 Exposure adjusted incidence rate estimates

5.2.4.1 Exposure adjusted incidence rate and 100*(1-α)% confidence interval

It will be assumed that for each of n subjects in a clinical trial the time t_j ($j=1, \dots, n$) to the first occurrence of a certain event is observed, or if the event was not experienced, the (censored) time to the end of the observation period. The sequence of first occurrences of an event will be modeled to follow approximately a Poisson process with constant intensity θ . The rate

parameter θ will be estimated as $\lambda = D/T$, where $T = \sum_{j=1}^n t_j$ and D is the number of subjects with

at least one event. Conditionally on T , an exact 100*(1-α)% confidence interval for a Poisson variable with parameter θT and observed value D can be obtained based on [Garwood \(1936\)](#), from which an exact 100*(1-α)% confidence interval for D/T will be derived as follows ([Sahai, 1993](#); [Ulm, 1990](#)):

Lower confidence limit $L = \frac{0.5c_{\alpha/2, 2D}}{T}$ for $D > 0$, 0 otherwise,

Upper confidence limit $U = \frac{0.5c_{1-\alpha/2, 2D+2}}{T}$

where $c_{\alpha, k}$ is the α th quantile of the Chi-square distribution with k degrees of freedom.

5.2.4.2 CRP Normalization Procedure

All CRP values referred to in this SAP constitute a STANDARDIZED CRP value to a NORMAL RANGE of 0 – 10 mg/L as per protocol (e.g. CRP value 20 mg/L normal value 0-20 mg/L will be transformed to 10 mg/L, nv 0-10 mg/L) as follows:

For the adapted ACR pediatric response, flare calculation, and for all instances in which CRP is necessary, the value coming from the local laboratory will be used. Local CRP will be standardized according to the following formula as per [Ruperto \(2005\)](#).

Standardization of laboratory tests: the CRP test results will be standardized based on the normal values provided by each local laboratory. All values will be converted to the international standard (SI) unit system (Laposata 1992), according to the following formulas:

$$x_{\text{ref}} = \left[(\text{range}_{\text{ref}} \times x_{\text{ref}100}) / 100 \right] + \text{min}_{\text{ref}},$$

where

- x_{ref} = value in the SI system,
- $\text{range}_{\text{ref}}$ = normal range of the SI system, and
- min_{ref} = minimum value in the SI system;

And

$x_{\text{ref}100} = [(x_i - \text{min}_{\text{OMU}}) / \text{range}_{\text{OMU}}] \times 100$, where

- x_i = value in the original measurement unit (OMU),
- $\text{range}_{\text{OMU}}$ = normal range of the OMU, and
- min_{OMU} = minimum value of the OMU.

For the purposes of the trial CRP will be normalized and the following normal range used:

x_{ref} = normalized value,

- $\text{range}_{\text{ref}}$ = normalized range of = 0 - 10 mg/dL,
- min_{ref} = minimum value = 0 mg/L;

For example, a CRP level of 2.5 mg/dl (OMU normal values 0.1–0.5 mg/dl) will be converted to 60 mg/L (Novartis normal values 0-10 mg/L).

$x_{\text{ref}} = [(\text{range}_{\text{ref}} \times x_{\text{ref}100}) / 100] + \text{min}_{\text{ref}}$,

$x_{\text{ref}100} = [(x_i - \text{min}_{\text{OMU}}) / \text{range}_{\text{OMU}}] \times 100$

$x_{\text{ref}100} = [(2.5 - 0.1) / 0.4] \times 100 = 600$

$x_{\text{ref}} = [(10 \times 600) / 100] + 0 = 60 \text{ mg/L}$

6 Reference

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